

FDA Issues a Final Rule on Substances Generally Recognized as Safe (GRAS) for Their Intended Use in Animal Food

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Animal Food and Drug

Nineteen years after first publishing its proposal, FDA published in yesterday's *Federal Register* its final rule on substances generally recognized as safe (GRAS) for their intended use in human and animal food.¹ This Alert addresses the final rule as it applies to food for animals. For an analysis of how the final rule will affect human food, see our Alert "[FDA Issues a Final Rule on Substances Generally Recognized as Safe \(GRAS\) for Their Intended Use in Food](#)".

Although the proposed regulations were published in 1997 and the FDA Center for Food Safety and Applied Nutrition (CFSAN) has been accepting GRAS Notification filings under a pilot program since that time, the FDA Center for Veterinary Medicine (CVM) did not launch its own pilot program until 2010.² In CVM's case, while the final rule in large part codifies the status quo, it also clarifies and potentially modifies some aspects of the CVM pilot program.

The final rule—through its preamble and the new regulations—will help companies understand when a substance is GRAS under the conditions of its intended use in animal food. The clarified GRAS criteria include:

- General recognition of safety requires “common knowledge,” throughout the expert scientific community knowledgeable about the safety of substances directly or indirectly added to food, that there is a reasonable certainty that the substance is not harmful under the conditions of its intended use;
- “Common knowledge” is based on “scientific procedures” or on experience based on common use of a substance in food prior to January 1, 1958; and
- A substance is GRAS under the conditions of its intended use only if it satisfies the safety standard for food additives under the Federal Food, Drug, and Cosmetic Act.

The final rule establishes requirements for how the GRAS conclusion should be structured and explained in a seven-part GRAS notice. FDA's detailed explanation of these seven parts will be helpful to anyone preparing a GRAS notice.

¹ 81 Fed. Reg. 54960 (Aug. 17, 2016).

² 75 Fed. Reg. 31800 (Jun. 4, 2010).

Background

Section 201(s) of the Federal Food, Drug, and Cosmetic Act (FDCA) describes the two most common types of ingredients in animal food: food additives and GRAS substances. Food additives require FDA approval before they can be marketed. GRAS substances do not. Both types are tied to their intended use. The same ingredient can be a food additive for one intended use and a GRAS substance for another.³

Section 201(s), which excludes a GRAS substance from the definition of “food additive” and related premarket approval requirements, describes a GRAS substance as one that is

generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown through scientific procedures (or, in the case of a substance used in food prior to January 1, 1958, through either scientific procedures or experience based on common use in food) to be safe under the conditions of its intended use.⁴

According to this definition, experts can generally recognize a substance as safe for use in animal feed and/or pet food through either (1) scientific procedures or (2) experience based on use in food prior to January 1, 1958. In the 1970s, FDA established procedures allowing it to affirm substances as GRAS by regulation. The procedures also allowed individuals to voluntarily submit to the agency a petition asking FDA to affirm the GRAS status of a substance under the conditions of its intended use in animal food.

In 1997, FDA proposed to establish in place of the labor-intensive GRAS petition/affirmation process a GRAS notification process, whereby sponsors would submit for FDA review a GRAS notice advising FDA that the sponsor had concluded the ingredient to be GRAS for a proposed use. If FDA does not disagree, the agency sends a letter to the sponsor stating that it has “no questions” regarding the sponsor’s GRAS conclusion.

Both the petition process and the notification process that replaced it have always technically been voluntary and an animal food manufacturer could, under the FDCA, conclude that a substance is GRAS and sell it on that basis without receiving approval, affirmation, or a “no questions letter” from FDA. This strategy has always been problematic for animal food, however, because animal feed, including pet food, and their ingredients are regulated primarily by the states and not solely by FDA. Therefore, state regulators can object to the use of ingredients that are not approved by either FDA⁵ or by the Association of American Feed Control Officials (AAFCO), which also has an animal feed ingredient approval system. The final GRAS rule does not change this dynamic.

³ In the preamble to the final rule, FDA explains that a GRAS notice can be an appropriate mechanism for informing the agency of a GRAS use for substance approved as a food additive for another use.

⁴ 21 U.S.C. § 321(s).

⁵ Many states will now accept as lawful for the intended use ingredients for which FDA has issued a “no questions letter” under the GRAS program, even though such ingredients are technically not “approved” by FDA.

Aspects of the Final Rule Especially Pertinent to Animal Food

Efficacy

The preamble discusses CVM's practice during its pilot GRAS program of requiring sponsors to provide data or information demonstrating the effectiveness or utility of a substance.⁶ Some comments claimed that the requirement to submit utility data generated from feeding studies is "inappropriate and unnecessary" as it does not relate to safety, the pivotal issue of the GRAS review.⁷ In response to these comments, CVM says it will require data and information on the substance's physical or other technical effect, including the quantity required to produce the effect, when necessary to demonstrate safety.⁸ CVM says that the typical approach to support the nutritive effect of a substance on the animal (as distinguished from a technical effect in the food) combines data about the general effects of the substance with feeding studies demonstrating that the substance acts as intended. If an appropriate study is not available in the literature, the sponsor could conduct and publish such a study. The agency notes, however, that there would be a time gap between such publication and the sponsor's ability to use the study to support a conclusion of GRAS status.⁹

Extrapolation between species

With respect to feeding studies, CVM advises that sponsors should consider whether a feeding study in one species or in one life stage of an animal can be used to support safety in another species or life stage. For example, because cattle have a fermentative digestive tract, it may be possible to extrapolate a cattle study regarding the bioavailability of selenium in selenium yeast to other species having a fermentative digestive tract. In contrast, it may not be possible to extrapolate the results of a cattle study of copper bioavailability to sheep because sheep have a much higher sensitivity to copper.¹⁰

Similarly, if information regarding exposure to a substance in a "worst case scenario" cannot be obtained from published literature, then data from a feeding study in one representative animal species may be sufficient for use to support a GRAS conclusion for multiple species if the species used in the feeding study represents a worst case scenario for exposure to the substance.¹¹

Safety in food-producing animals

For substances to be used in feed for food-producing animals, GRAS conclusions must be based not only on safety in the target animal but also on safety in the humans who consume it. In addition to identifying and providing supporting information for quantities of any substance expected to be formed in or on the animal feed, the sponsor must also provide the potential

⁶ 81 Fed. Reg. at 55032.

⁷ *Id.*

⁸ *Id.*

⁹ *Id.* at 55033.

¹⁰ *Id.* at 55034.

¹¹ *Id.* at 55035.

quantities, plus supporting data and information, of any residues to which humans may be exposed in edible animal tissues.¹²

Drinking water

The final rule provides that “animal food” includes drinking water for the purposes of a GRAS analysis.¹³

Sponsor contacts

Some comments claimed that CVM’s pilot program differed from CFSAN’s in that CVM did not contact a sponsor to discuss the agency’s questions after it had accepted a GRAS notification for filing. One comment said that CVM had “informally indicated that once a GRAS notice is accepted for filing, there will be no further communication with the notifier and the GRAS notice will be judged solely on what was accepted for filing.”¹⁴ CVM disagrees with these comments. According to the agency, it contacted the sponsors of nine of the eighteen GRAS notices it reviewed during the pilot period, and it issued “no questions letters” for seven of those nine notices after the sponsors provided clarifying amendments.¹⁵ CVM points out that the text in CVM’s section 570.265 regulation is the same as that in CFSAN’s section 170.265 regulation governing what each respective center will do with a GRAS notice, and it says it intends to consider the same factors that CFSAN considers on several issues including when it contacts a sponsor during a GRAS notification review.¹⁶

What It Means to be GRAS

The final rule discusses what it means to be GRAS, including the data that must be considered in reaching a GRAS conclusion. A GRAS conclusion depends on “common knowledge,” which must be based on either scientific procedures or experience of common use before 1958. The same safety standard that would be required to support a food additive regulation—“reasonable certainty of no harm”—must underpin a conclusion of GRAS status, though the evidence to meet that standard can be different. A GRAS conclusion must be based primarily upon publicly available data on both safety and exposure, whereas a food additive petition may be based upon non-public proprietary data.

A GRAS conclusion hinges on “common knowledge,” gleaned either through scientific procedures or based on common use before 1958

A GRAS conclusion—general recognition of safety—requires “common knowledge” about an ingredient’s safety:

General recognition of safety requires common knowledge throughout the scientific community knowledgeable about the safety of substances directly or indirectly added to food that there is reasonable certainty that the substance is not harmful to either the

¹² *Id.* at 55037.

¹³ *Id.* at 55035.

¹⁴ *Id.*

¹⁵ *Id.* at 55038.

¹⁶ *Id.* at 55037-8.

target animal or to humans consuming human food derived from food-producing animals under the conditions of its intended use.¹⁷

Common knowledge can be based either on “scientific procedures” or on experience based on common use of a substance in food prior to January 1, 1958.

Scientific procedures

If common knowledge is established through scientific procedures, it must be based upon the application of generally available and accepted scientific data, information, or methods, which are ordinarily published, as well as the application of scientific principles. Under the final rule, scientific procedures include scientific data, information, methods, and principles appropriate to establish the safety of a substance.

Under the final rule, recognition of safety based on scientific procedures requires the “same quantity and quality of scientific evidence as is required to obtain approval of a food additive.”¹⁸ FDA advised that it intends to issue guidance to further clarify that food substances should be evaluated for safety in the same way regardless of whether they are food additives or GRAS substances for a given use.

Experience of common use before 1958

General recognition of safety through experience based on common use in food prior to January 1, 1958, must address safety for both the target animal and for humans consuming human food derived from food-producing animals. With respect to animal species, common knowledge based on pre-1958 use must be based solely on food use of the substance in the same animal species and will ordinarily be based on generally available data and information.¹⁹

Safety must be to a “reasonable certainty”

Under section 570.3(i), “safe” and “safety” is defined as “a reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use.”²⁰ In the preamble, FDA equates this standard to the standard for food additives:

Congress recognized that, under [the Food Additives Amendment], the safety of a food additive could not be established with absolute certainty, and thus provided for a science-based safety standard that requires sponsors of food additives to demonstrate to a reasonable certainty that no harm will result from the intended use of an additive. We have incorporated this safety standard into our regulations for food additives and GRAS substances.²¹

In the other words, GRAS substances are neither safer nor less safe than approved food additives.

¹⁷ 21 C.F.R. § 570.30(a).

¹⁸ 21 C.F.R. § 570.30(b).

¹⁹ 21 C.F.R. § 570.30(c)(1).

²⁰ 21 C.F.R. § 570.3(i).

²¹ 81 Fed. Reg. at 54963.

A GRAS conclusion must rely on public data on safety and exposure

A substance is GRAS under its intended conditions of use only if qualified experts can reach that conclusion. According to FDA, experts can reach the conclusion only if critical information is public. Whether a person submits a GRAS notice or not, the data and information that it relies upon for a GRAS conclusion must be public. Publication in peer-reviewed scientific journals is best, but FDA will also accept other types of public information, including publication in a textbook or technical literature such as the publications of the Joint Expert Committee on Food Additives (a joint committee of the Food and Agriculture Organization and World Health Organization).

In addition to safety data, exposure data must also be publicly available. The rule clarifies that exposure data is relevant for all GRAS conclusions, whether based on scientific procedures or pre-1958 use. Such data must now be included in all GRAS notices.

Non-public information can be “corroborative”

While the GRAS conclusion must hinge on public data, non-public data can be corroborative. Such data can support a GRAS conclusion, but they must not be necessary to it.

Non-public information includes unpublished data, information, and methods. It includes trade secrets and confidential commercial information. If a person chooses to submit a GRAS notice, it can put trade secrets and confidential commercial information only in certain sections of the notice, reflecting the lower weight such information can bear in a GRAS conclusion.

An opinion of a GRAS panel can be evidence of general recognition

A GRAS panel, a panel of individuals who evaluate whether the data establish that a substance is GRAS for its intended use, is not necessary to a GRAS conclusion. FDA considers a GRAS panel one among many ways to demonstrate consensus. In the preamble, it says: “[C]onvening a GRAS panel has historically been a way to provide evidence that generally available data and information are generally accepted by the expert scientific community, but convening a GRAS panel is not the only way to provide such evidence.”²²

According to the preamble, FDA will consider an opinion of a GRAS panel “to be part of the secondary scientific literature” and thus something that “could provide evidence that the data and information discussed in the publication are generally accepted.”²³ The weight of a GRAS panel’s opinion would depend on factors such as the subject matter expertise of its members.

One issue that often comes up with a GRAS panel is potential conflicts of interest. FDA announced that it will issue guidance on conflicts of interest—first a draft guidance, then a final one after a comment period, though it has not announced a time frame for the release of these documents.

²² *Id.* at 55026-27.

²³ *Id.* at 54974.

What a GRAS Notice Should Contain

The final rule will be particularly helpful to persons preparing a GRAS notice. While the proposed rule did not specify individual parts for a GRAS notice, the final rule imposes requirements for any GRAS notice that is submitted to FDA. Specifically, each GRAS notice must contain the following seven parts:

1. **Signed Statements and Certification.** This part should include information about trade secrets, intended conditions of use, and the basis for the conclusion of GRAS status.
2. **Identity, Method of Manufacture, Specifications, and Physical or Technical Effect.** This part should include information necessary to characterize the substance well and to understand the method of manufacture.
3. **Target Animal and Human Exposure.** This part should include information about the exposure to the target animal and to humans consuming human food derived from food-producing animals, regardless of whether the conclusion of GRAS status is through scientific procedures or through experience based on common use in food.
4. **Self-Limiting Levels of Use.** This part should describe circumstances where the amount of the notified substance that can be added to food is limited because the food containing levels of the notified substance above a particular level would become unpalatable or technologically impractical.
5. **Common Use in Food Before 1958.** For common use in food to be the basis for the GRAS conclusion, the pre-1958 consumption must be by a significant number of animals of the species to which the substance is intended to be fed and by humans consuming foods derived from food-producing animals.
6. **Narrative.** This part should describe the basis for the conclusion of GRAS status.
7. **Supporting Data and Information.** This part should specify which of these data and information are generally available and which are not.

FDA commits to responding to GRAS notices in a reasonable time, typically 180 days. The regulations allow FDA to extend this timeframe by 90 days as needed. If FDA opts for an extension, it will inform a sponsor within 180 days of filing. Under the final rule, a sponsor can amend a GRAS notice before FDA responds to it, and/or supplement it after the agency responds.

“No questions” will continue, at least for now

In the preamble to the final rule, FDA suggests that it will generally continue to respond to GRAS notices in one of three ways:

1. With a “no questions letter” when it does not have a concern about the safety of a substance;
2. With an “insufficient basis letter” when a GRAS notice does not provide a basis for a conclusion that the notified substance is safe under the conditions of its intended use (including when critical information is not public);
3. With a “cease to evaluate letter” when the sponsor requests that FDA stop evaluating the GRAS notice.

Conclusion

The final rule formalizes the voluntary GRAS notification procedure under which the animal food industry has operated since 2010, while modifying certain requirements for such notifications. It also provides the agency's current view on what constitutes general recognition of safety and what should go into a GRAS conclusion. The final rule, including its preamble, will provide a useful guide for all companies who seek to use GRAS substances in their animal food products.

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